REMARKS

Amendments To the Claims

Claims 1-16, 18-23, 25-26, 30-31 and 33-46 were canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional application.

Claims 17 and 29 have been amended to recite the specific doses of the compound administered. The support for the amendment is found at paragraph [0066] of the published application. Upon entry of the present amendments, claims 17, 24, 27-29, 32 and 47 are pending in this application. No new matter has been introduced by the amendments, and their entry is respectfully requested.

Claims Rejection under 35 U.S.C. §103

1. The cited reference would not have provided any reason to select the claimed compound for the treatment of claimed disease.

Claims 17, 24, 27-32 and 47 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,877,200 ("Muller"). Pages 2 of Office Action. Applicant respectfully disagrees.

The current standard of obviousness requires that the PTO establish (1) that there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) that there would have been a reasonable expectation of success. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007). The USPTO has not met this standard in this case.

The instant claims recite the use of compound, enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-isoindolin-2-yl)-propionamide at the dose range of from about 800 mg to about 1,200 mg per day for treatment of Crohn's Disease. In other words, the claims recite the administration of a specific compound for the treatment of a specific disease at a specific dose. The PTO fails to establish that each of these claim limitations is taught or suggested in the prior art. *See, e.g. In re Ochiai*, 71 F.3d 1565, 1571 (Fed. Cir. 1995) (all of the claim limitations must be taught or suggested by the prior art.).

The PTO alleges that Muller discloses "the selection of a particular compound and particular disease in a clear manner allowing the skilled in the artisan to practice

the invention of Muller, however broadly disclosed, in an effective manner." Page 3 of Office Action. Applicant respectfully disagrees.

Muller discloses several genera of compounds represented by general Formulas I (IA, IB and IC) and II (IIA, IIB and IIC) (Columns 4-8), which can be replaced by various substituents at various positions, and discloses many specific compounds in Examples 1-101. The combinations of the possible substituents (*e.g.*, Z, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{8'}$, $R^{9'}$, R^{10}, and R^{12}) in Formulas I and II would lead to thousands of compounds (Columns 4-8). While Muller discloses the racemic compound of the isomer recited in the claims herein [in Example 42], the mere fact that a species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *See, e.g.*, *Sanofi v. Apotex* 492 F.Supp.2d 353 (S.D.N.Y. 2007); *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *In re Brouwer*, 77 F.3d 422, 425, 37 U.S.P.Q.2d 1663, 1666 (Fed. Cir. 1996); MPEP § 2144.08.

Applicant respectfully submits that the Examiner does not appear to appreciate that the genus disclosed in the cited reference encompasses thousands of compounds. As well settled, the legally required "reason" to select a species or subspecies from a genus for purposes of 35 U.S.C. §103 does not exist unless there was "[s]ome motivation to select the claimed species or subgenus [from] the prior art." (*In re Deuel*, 51 F.3d 1552, 1558-9, 34 USPQ2d 1210 (Fed. Cir. 1995) ("No particular one of these DNA's can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.") (emphasis added); *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994) ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences corresponds to [a gene], the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."); *see also* MPEP §2144.08). This principle has not changed after the *KSR* decision, as evidenced by the Federal Circuit's decision in *Takeda. Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350 (Fed. Cir. 2007). In *Takeda*, the Court held that it was not obvious to select one compound out of a prior art reference that disclosed a large amount of compounds, in part, because "[r]ather than identify predictable solutions...the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." ((*Id.* at 1359 (emphasis added)).

In the instant case, similar to *Takeda*, "rather than identify predictable solutions," Muller discloses a genus that encompasses a large number of compounds, "any one of which could have been selected as a lead compound for further investigation." *Id.* Moreover, similar to *Baird*, "[a]bsent anything in the cited prior art suggesting which of the [many] possible [compounds] corresponds to [the claimed compound]," the PTO has not met its burden of establishing that the prior art would have suggested the [claimed compound]." (*Baird*, 16 F.3d at 380). As such, even if the racemate of the instant compound were encompassed by a genus of Muller, it would not have been obvious to select the racemate, much less its isomer (see below). Indeed, the fact that Muller discloses a broad genus alone renders the PTO's rejection under 35 U.S.C. §103 improper. *See, e.g., Sanofi v. Apotex* 492 F.Supp.2d 353 (S.D.N.Y. 2007); *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *In re Brouwer*, 77 F.3d 422, 425, 37 U.S.P.Q.2d 1663, 1666 (Fed. Cir. 1996); MPEP § 2144.08.

To the extend one of ordinary skill in the art would have been led to select the compounds of Muller, they may very well look at different compounds (such as 3-phenyl-3-(1-oxoisoindolin-2yl)propionamide, as disclosed as a typical embodiment in Abstract) or their modifications, as opposed to the racemate of Example 42. Thus, Muller viewed as a whole does not focus on this racemic compound among the thousands of compounds recited therein, much less its isomer. In sum, Muller does not provide one of ordinary skill in the art with any reason to single out the specific racemate to which the recited enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide belongs.

With regard to selecting the isomer, the Federal Circuit specifically addressed the issue of whether a single enantiomer of a compound can be nonobvious in view of a prior art disclosure of that compound's racemate and affirmed the patentability of chiral pharmaceutical compounds. (*See e.g., Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007), *aff'g* 438 F.Supp.2d 479; *Sanofi-Synthelabo v. Apotex*, 470 F.3d. 1368 (Fed. Cir. 2006); *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004)). It is also well known to those of ordinary skilled in the chemical and pharmaceutical arts that the separation and/or preparation of specific isomers is not predictable, nor are these processes always routine. (*Id* at 493; *see also* J. Darrow, *The Patentability of Enantiomers:*

Implications for the Pharmaceutical Industry, 2007 Stanford Tech. L. Rev. 2, ¶56 ("the process for making the racemate may not make obvious a process for resolving the racemate.")). Further, whether a specific stereoisomer has improved biologically activity or a more desirable pharmacological profile is recognized as unpredictable in the art. (*See In Re May* at 1092; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, at 754 (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer); *see also Ex Parte Bonfils*, 64 U.S.P.Q.2d 1456, 1461 (B.P.A.I. 2002)).[1]

Muller provides no preference for the biological or pharmacological activity of the racemic compound, much less any indication of the activity of the specific enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-isoindolin-2-yl)-propionamide for treating Crohn's Disease within the instant claims. Without such specific guidance in the cited art, one of ordinary skill in the art would not have had any reason to select the specific enantiomerically pure (-)-isomer recited in the instant claims. Without such a reason, a *prima facie* case of obviousness cannot be made. (*See KSR*, 127 S.Ct. at 1742; *Takeda,* 429 F.3d at 1359.) Thus, even assuming, *arguendo*, that one of ordinary skill in the art would have selected the racemate of the recited compound, Applicant respectfully submits that the instant claims, which specifically recite the use of the enantiomerically pure (-)-isomer for treating Crohn's Disease at the specific doses, are not obvious by Muller.

Nonetheless, in supporting the alleged obviousness, the Office has stated that "insofar as the specific compound and the specific disease are clearly and unquivocally disclosed," one skilled in the art would have been motivated to select the specific compound and the specific disease. Page 3 of Office Action. As discussed above, Muller does not focus on the specific isomer recited in the pending claims. Further, Muller discloses that more than thirty diseases/conditions are associated with TNFα production. However, the PTO alleges that Muller teaches each compound to be effective for each disease, and that this would have been easily accepted by one of ordinary skill in the art. *Id.* If this assertion were true, any and all compounds having TNF-α activity would be obvious to use in treating Crohn's Disease. In other words, the PTO appears to be making the broad generalization that it would be obvious to

[1] *Bonfils* is a nonprecedential decision.

treat any disease or disorder associated with TNF-α with any compound disclosed to be a TNF-α inhibitor, regardless of the thousands of possible variations thereof. *Id.* Clearly, this rejection is wholly inconsistent with the current standard of obviousness. Indeed, the mere "identification in the prior art of each component of [an invention] does not show that the combination as a whole...is obvious." *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Rather, "the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention." *Id.* (Emphasis added). The PTO's bare allegation that Muller provides motivation to select the specific compound and the specific disease merely because it discloses the compound and the disease does not meet the legal requirement for a *prima facie* case of obviousness. *Takeda* at 1359.

2. The cited reference would not have provided the legally required reasonable expectation of success.

Applicant respectfully submits that even if it is assumed, *arguendo*, that the broad teaching would have provided the alleged motivation to use a specific compound at a specific dose for the treatment of a specific disease, such a motivation is not enough to support a legally proper rejection under 35 U.S.C. §103. A reasonable expectation of success must also be found from the reference. The broad teachings from the cited reference would not have provided a reasonable expectation of success for using the enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide for the specific treatment of Crohn's Disease, much less at the specifically claimed dosages. The Federal Circuit, following the landmark case of *KSR*, reaffirmed the guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious" as previously set forth by the same Court. *PharmaStem*, 491 F.3d at 1364. As the Federal Circuit explained:

> an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id., citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (internal quotations omitted) (emphasis added); *see also* MPEP §2145(X)(B).

In the instant case, to arrive at the claimed methods, not only would one skilled in the art have had to try each of numerous possible choices of variables from the genus of Muller, but one skilled in the art would have also have had to try each of numerous possible choices of TNF-related disorders. Taking all of the claim limitations into consideration, *i.e.*, the specific compound, the specific disease, and the specific dose, one skilled in the art at the time of the invention, having only the cited reference as guidance, would have had to first randomly try all possible substituents until arriving at the recited enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, then randomly try all diseases until arriving at Crohn's Disease, and then randomly try dosages until arriving at the claimed dosage of about 800 mg to about 1,200 mg per day, which are not disclosed or suggested in the reference. This type of guidance can only amount to "general guidance"[2] and is exactly what the Federal Circuit warned is not a legally sufficient "reasonable expectation of success." *Id.* The reference would not have provided any indication as to why there should be an expectation of success in specifically treating Crohn's Disease with the instant compound, even less treating the specific disease with the specifically claimed dosages of the compound. Under the standard articulated above for a reasonable expectation of success, these types of broad teachings or general guidance would not have provided a reasonable expectation of success for the claimed methods. Thus, the rejection should be withdrawn.

3. Unexpected results rebut even a *prima facie* case of obviousness.

The PTO alleges that there is no objective proof for any therapeutic properties of the recited enantiomer that would have been unexpected from Muller. Page 4 of Office Action. The PTO further alleges that it is not seen to be unobvious that one enantiomer exhibits different results than the other enantiomer, and that the skilled in the art would have expected that each enantiomer would have exhibited different results such that the totality of results provided by the combination of each enantiomer would have been expected from the results displayed by each enantiomer.

[2] The Office Action itself refers to the teachings relied upon in the obviousness rejection as broad disclosures. Office Action, page 3.

Page 5 of Office Action. The Examiner further alleges that additive results of specific enantiomers are not unexpected. *Id.* Applicant respectfully disagrees.

As well settled, even if a *prima facie* case of obviousness is established, the Examiner is required to consider all rebuttal evidence submitted by an applicant. *See In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *see also* MPEP §2145. This requirement remains unchanged following the decision in *KSR*, as the Federal Circuit has made clear in *In re Sullivan*. at 1351. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *Id.* at 1351. Such rebuttal evidence includes "evidence of unexpected results." *Id.*, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007).

As noted in Applicant's Response of February 13, 2008, even assuming, *arguendo*, a *prima facie* case of obviousness were established, there is evidence of unexpected results for the activity of the instant compound that rebuts any such *prima facie* case. That is, Applicant submitted that the experimental results showed that the instant (-)-enantiomer possesses IC_{50} of TNFα inhibition (3μM) which is seven times less than that of the racemic compound (21μM), 30 times less than that of the opposite enantiomer (100μM) (Example 3 on page 41 of the specification); IC_{50} of PDE4 inhibition (4.4μM) which is almost four times less than that of the racemic compound (15μM), 15 times less than that of the opposite enantiomer (67μM) (Example 4 on page 42 of the specification); PDE 4 inhibition selectivity (>33) which is about six times higher than the racemic compound (>4.8), more than 32 times higher than the opposite enantiomer (~1) (Example 5 on page 43 of the specification); and higher plasma concentration and AUC than the racemic compound (Example 6 on page 43 of the specification). Thus, the (-)-enantiomer recited in the instant claims showed not only superior effect of TNFα inhibition, but also superior effects of PDE4 inhibition, PDE4 selectivity and pharmacokinetic properties. The cited reference has not provided any of these results.

Applicant respectfully submits that these results are sufficient to rebut any presumption of obviousness that may have been established by the reference cited in the Office Action. *Sanofi-Synthelabo*, 470 F.3d. at 1380; *In re May*, 574 F.2d 1082 (C.C.P.A. 1978). As noted above, as a matter of law, the Examiner must consider evidence of unexpected results. *In re Sullivan*, 498 F.3d at 1351. Be that as it may, Applicant maintains the position that the presented data provide sufficient evidence of

unexpected results to rebut any presumption of obviousness. Thus, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

CONCLUSION

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendments and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: September 19, 2008

Yeah-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778